Emerging Implications of Genetic Testing in Inherited Primary Arrhythmia Syndromes

Babken Asatryan, MD, and Argelia Medeiros-Domingo, MD, PhD

Abstract: Inherited primary arrhythmia syndromes are genetically determined disorders of cardiac ion channels or ion channel macromolecular complexes usually associated with a higher risk of sudden cardiac death. These conditions have a very broad spectrum of clinical manifestations, ranging from an asymptomatic course to syncope, atrial and ventricular arrhythmias, and conduction disturbances, but may produce sudden infant death syndrome and unexplained sudden cardiac death in apparently healthy individuals. During the last 20 years, the evolving knowledge on the genetic basis of inherited arrhythmia syndromes has dramatically reshaped our understanding of these conditions and, consequently, had a great impact on patient care. Based on the knowledge of the genetic substrates, specific risk factors for individual genotypes have been identified, and various investigations have been launched with the intention of developing a gene- and even mutation-specific therapy. Preliminary results from animal studies suggest that gene therapy rescues the normal ion channel function and thereby prevents cardiac events in some primary arrhythmia syndromes, which suggests that upon appropriate validation in a clinical setting, it may become available for affected patients. The purpose of this review is to provide clinicians with a contemporary insight into the role of genetic testing in the diagnosis, therapy, and prognosis of patients with primary arrhythmia syndromes, and the clinical implications of screening family members who are at risk of sudden cardiac death.

Key Words: arrhythmia, ion channels, genetics, sudden death

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Inherited primary arrhythmia syndromes are genetically determined cardiac diseases caused by mutations in genes encoding cardiac ion channels and associated regulatory proteins (Fig. 1).[1] These disorders usually follow the Mendelian inheritance pattern, frequently present in the early years of life, and can cause cardiac arrest and/or sudden cardiac death (SCD) among young and apparently healthy individuals.[2] Genetic testing in these diseases has important implications in diagnosis, prognosis, and therapy.[1,3] Important features of cardiac channelopathies are variable clinical phenotype and variable expression of the disease in which vulnerability to arrhythmias and disease progression is determined by the multifaceted interplay of the mutation characteristics, epigenetic and environmental factors.[4] Many of these diseases exhibit overlapping phenotypes, and the precise genetic diagnosis allows specific therapy. The recent advances in next-generation sequencing technologies have provided clinicians and researchers with unique tools to better understand the genetic aspects of these diseases. Here we summarize the current knowledge on genotype–phenotype associations in inherited arrhythmia syndromes, with a focus on important clinical implications of the genetic test in the management of affected patients and their relatives. Due to their controversial impact on clinical application, we did not include in this review the genetic basis of atrial fibrillation (AF) and idiopathic ventricular fibrillation (VF).

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LONG QT SYNDROME

The congenital long QT syndrome (LQTS) is a genetically determined cardiac arrhythmia syndrome characterized by a prolongation of the QT interval on the electrocardiogram (ECG) and an increased propensity to syncope, seizures, polymorphic ventricular tachycardia (VT) (typically, torsades de pointes), cardiac arrest, and SCD in individuals with structurally normal hearts (Fig. 2).[5,6] The prevalence of congenital LQTS is estimated in the range of 1:2000–1:2500.[7]

Diagnosis of LQTS

The diagnosis of LQTS relies on symptoms, QT interval duration in the 12-lead ECG corrected for heart rate (QTc), clinical and family history, and genetic test results.[8] Based on these parameters, Schwartz and Crotti[9] proposed a scoring system that allows determining the probability of having LQTS (Table 1).[9] Currently, LQTS is diagnosed in the presence of a QTc interval ≥500 milliseconds, an unequivocally pathogenic mutation in one of the LQTS genes, or a LQTS risk score ≥3.5 in the absence of secondary causes of QTc prolongation.[8] The diagnosis can also be made in the presence of a QTc between 480 and 499 milliseconds in repeated ECGs in a patient with unexplained syncope, in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation.[3,8] The diagnosis or exclusion of LQTS solely relying on QTc values should be avoided because nearly 30% of patients hosting pathogenic mutations in LQTS genes display normal QTc intervals; thus, the Schwartz criteria are an invaluable tool for the selection of candidates for further testing.[10]

Genetics Basis of LQTS and Implications of the Genetic Test in LQTS

To date, 16 genes have been associated with LQTS (Supplementary Table 1, http://links.lww.com/CIR/A15). The major LQTS genes are *KCNQ1* (LQTS1), *KCNH2* (LQTS2), and *SCN5A* (LQTS3), which collectively account for approximately 90% of all genotype-positive cases.[11] Nearly 8% of LQTS patients host compound heterozygous mutations.[12] Thirteen minor LQTS genes together explain approximately 5–10% of cases. These include 3 genes that cause multisystem syndromic disorders associated or not associated with prolonged QTc values: ankyrin-B syndrome (*ANK2*, LQTS4), Andersen–Tawil syndrome (ATS) (*KCNJ2*, LQTS7), and Timothy syndrome (*CACNA1C*, LQTS8).

Diagnostic Value

The yield of genetic testing in LQTS reaches 70–80% (Fig. 3).[13] Identification of a clear LQTS-associated mutation in any major gene

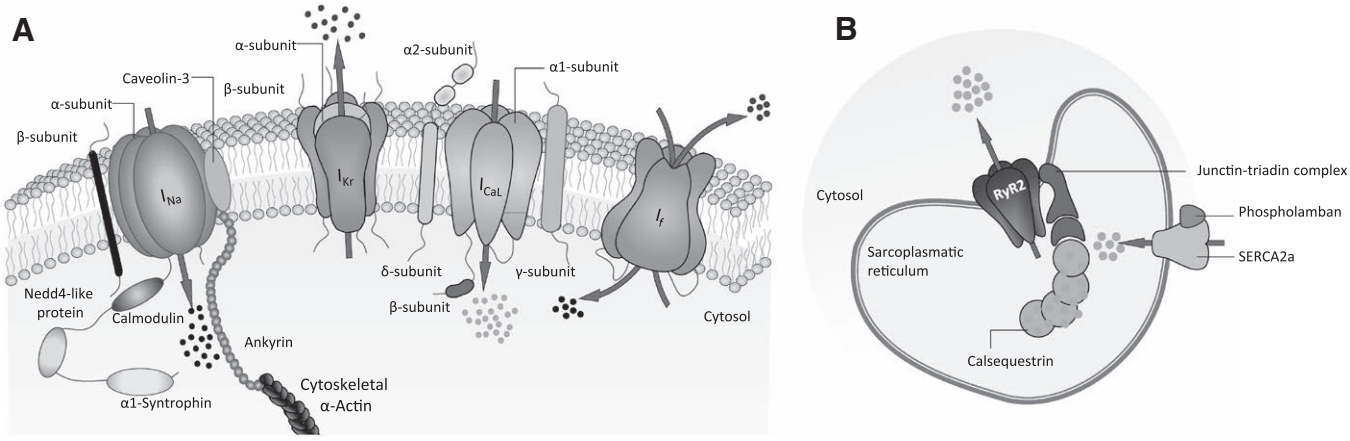

FIGURE 1. Schematic representation of cardiomyocyte ion channel structural elements implicated in the pathogenesis of the cardiac channelopathies. A, The main membrane channels responsible for cardiac action potential. B, Sarcoplasmic calcium-release complex. ATP indicates, adenosine triphosphate; I_{CaL}, calcium current; I_{Na}, sodium current; I_{Kr}, rapid component of the delayed rectifier potassium current; I_f, pacemaker ('funny') current; SERCA2a, sarcoplasmic/endoplasmic reticulum calcium ATPase 2a.

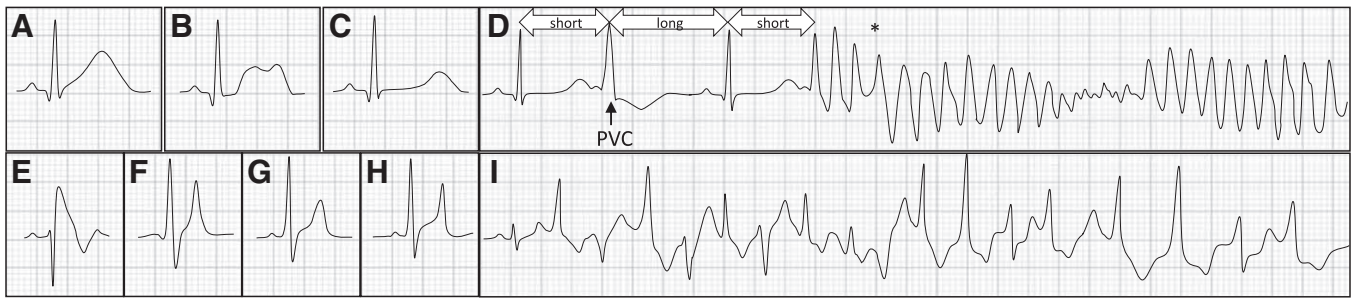

FIGURE 2. Characteristic ECG patterns in inherited primary arrhythmia syndromes. Long QT syndrome type 1–3 (A–C), and torsades de pointes (D); Brugada syndrome (E); short QT syndrome type 1–3 (F–H); and polymorphic (bidirectional) ventricular tachycardia in response to increased exercise load, characteristic for catecholaminergic polymorphic ventricular tachycardia (I). Note the characteristic features of the torsades de pointes arrhythmia: the prolonged QT interval with distorted T-U complex, the arrhythmia initiating short-long-short ventricular cycle sequence triggered by a PVC, the "warm-up" phenomenon with initial R-R cycles longer than subsequent cycles, and the abrupt switching of QRS morphology from predominately positive to predominately negative complexes (*). ECG indicates electrocardiogram; PVC indicates premature ventricular contraction.

is considered diagnostic, regardless of QTc duration (Table 2). The overall penetrance (proportion of mutation carriers who develop the disease) is estimated to be nearly 40%[14] but is reported in the range of 25–100% among different LQTS subtypes and dependent on mutation localization.[15–18] Genotyping is particularly important in patients with a high probability of LQTS (Schwartz score, >3).[1] However, the clinical diagnosis of LQTS will not be swayed by a negative genetic test, which occurs in 20% of "unquestionable LQTS" (Schwartz score, ≥3.5) cases because these patients have a lower risk for arrhythmias than the genotype positives, but have a considerable risk for arrhythmic events.[19]

Genotype–Phenotype Correlation

LQTS1 (*KCNQ1*), LQTS5 (*KCNE1*), and LQTS11 (*AKAP9*) are caused by defective I_{Ks}, the slow component of the delayed rectifier potassium current (I_K). *KCNQ1* and *KCNE1* genes encoding respectively the α and β subunits of the voltage-gated potassium channel, which conducts the I_{Ks} current, whereas A kinase anchoring protein 9 (*AKAP9*) facilitates the phosphorylation of *KCNQ1* by protein kinase A and thereby augments the I_{Ks} current. *KCNQ1* is the most common cause of LQTS and accounts for 30–35% of all genotype-positive cases. Homozygous or compound heterozygous mutations in *KCNQ1* or *KCNE1* produce autosomal recessive Jervell–Lange–Nielsen syndrome, characterized by severe LQTS phenotype, as evidenced by a QTc >500 milliseconds, a high rate of sudden death, and sensorineural deafness.[20] Patients with LQTS1 typically have a QTc prolongation and broad-based T wave on resting ECG.[21] *KCNQ1* mutations also account for over 90% of fetal bradycardias.[22] Mutations in *KCNQ1* predispose affected individuals to arrhythmias during times of physical (62%) or emotional duress (26%) owing to the inability of the cardiomyocytes to adopt (shorten) the repolarization duration to the rising heart rate due to defective I_{Ks} current.[23]

LQTS2 (*KCNH2*) and LQTS6 (*KCNE2*) are caused by defective I_{Kr} current, the fast component of I_K. *KCNH2* and *KCNE2* encode respectively the α (*HERG*) and β subunits MinK-related peptide 1 (MIRP) of the potassium channel that generate the I_{Kr} current.[24,25] *KCNH2* mutations explain nearly 25–30% of LQTS cases. The ECG is remarkable for a low-amplitude, notched or biphasic T wave (Fig. 2)[21] but may be normal in 20% of *KCNH2* mutation carriers.[10] Patients with LQTS2 often present with syncope and cardiac arrest in response to emotional stressors (43%), including unexpected auditory stimuli such as sudden noises and

TABLE 1. Updated Diagnostic Criteria for Long QT Syndrome Proposed by Schwartz et al[9]

	Points
Electrocardiographic findings*	
A. QTc† (ms)	
≥480	3
460–479	2
450–459 (in males)	1
B. QTc† at the fourth minute of recovery from exercise stress test ≥480 ms	1
C. Torsade de pointes‡	2
D. T wave alternans	1
E. Notched T wave in 3 leads	1
F. Low heart rate for age§	0.5
Clinical history	
A. Syncope‡	
With stress	2
Without stress	1
B. Congenital deafness	0.5
Family history	
A. Family members with definite LQTS¶	1
B. Unexplained sudden cardiac death <30 years of age among immediate family members¶	0.5

Score: ≤1 point, low probability of LQTS; 1.5–3 points, intermediate probability of LQTS; and ≥3.5 points, high probability.

*In the absence of medications or disorders known to affect these electrocardiographic features.

†QTc calculated by Bazett's formula where $QTc = QT / \sqrt{RR}$.

‡Mutually exclusive.

§Resting heart rate below the second percentile for age.

¶The same family member cannot be counted in A and B.

LQTS indicates long QT syndrome; QTc, QT interval duration in the 12-lead electrocardiogram corrected for heart rate.

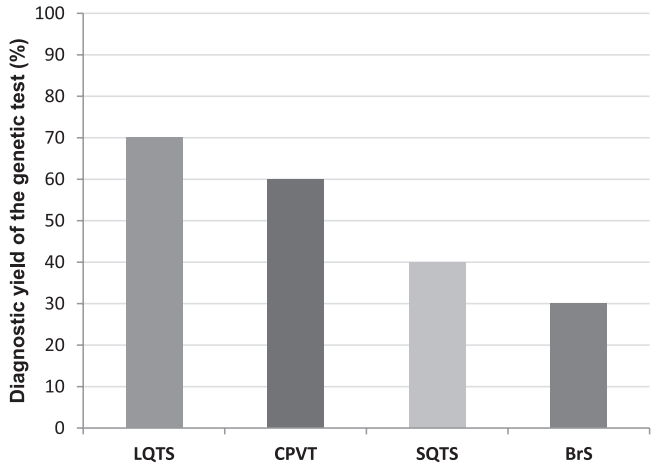

FIGURE 3. Diagnostic yield of the genetic test in primary arrhythmia syndromes. The yield in progressive cardiac conduction disease is not well determined and is therefore not provided. BrS indicates Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; LQTS, long QT syndrome; SQTS, short QT syndrome.

telephone ringing (26%), particularly when occurring at rest (64%).[23] An association of LQTS2 with seizures has been documented.[26] Women with LQTS2 are particularly at risk in the postpartum period, and during the menopause transition and postmenopausal periods.[27] In contrast to LQTS1, arrhythmias in LQTS2 are rarely triggered by exercise (13%) and occur twice more frequently while at rest or asleep (29%).[23]

TABLE 2. Summary of the Clinical Implications of Genetic Testing in the Management of Patients With Primary Arrhythmia Syndrome and Screening of Their Relatives

	Diagnostic Value	Prognostic Value	Therapeutic Implications	Family Screening
LQTS	+	+	+	+
CPVT	+	+	+	+
BrS	+/–	+/–	–	+
SQTS	+/–	–	–	+
PCCD	+	+/–	+	+

Detailed information on clinical implications and appropriate references can be found in the text.

BrS indicates Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; LQTS, long QT syndrome; PCCD, progressive cardiac conductance disease; SQTS, short QT syndrome.

There are few cases of LQTS6 reported in the literature; however, no genotype–phenotype segregation has been documented. A recent study has found that *KCNE2* variants may be insufficient in isolation to cause LQTS but may confer proarrhythmic susceptibility when provoked by additional QTc modifiers.[28]

LQTS3 (*SCN5A*), LQTS9 (*CAV3*), LQTS10 (*SCN4B*), and LQTS12 (*SNTA1*) are caused by defective inward late sodium current (I_{Na}). $Na_V1.5$ cardiac sodium channel, encoded by *SCN5A*, conducts the I_{Na} current responsible for phase 0 depolarization.[29] LQTS3 is caused by heterozygous gain-of-function mutations in the *SCN5A* and accounts for 5–10% of genotype-positive LQTS cases. LQTS3 penetrance reaches 90%.[30] Gain-of-function mutations in *SCN5A* prolong the QT interval via small net increase in the I_{Na} current. Patients with LQTS3 often experience arrhythmias and cardiac arrest while at rest (39%), particularly during sleep when increased vagal tone favors slower heart rate.[23] In these patients, prolongation of the ST-segment accounts for QT prolongation and is typically followed by a T wave of relatively small amplitude (Fig. 2).[21]

LQTS4 (*ANK2*) is caused by defective ankyrin-B protein. Loss-of-function mutations in *ANK2* abolish the ability of ankyrin-B to restore abnormal calcium dynamics and abnormal localization and expression of Na/Ca exchanger, Na/K adenosine triphosphate (ATPase), and inositol trisphosphate receptor in cardiomyocytes.[31] These functional impairments lead to calcium accumulation in the cytoplasm and cause early and delayed after-depolarizations, typically in response to catecholaminergic stimulation. These malfunctions produce varying degrees of cardiac dysfunction, bradycardia, sinus arrhythmia, bidirectional VT, VF, and risk of sudden death, collectively called "ankyrin-B syndrome." These patients have inconsistent and variable QTc prolongation, indicating that ankyrin-B syndrome represents a separate clinical entity with features overlapping with LQTS (LQTS4) and catecholaminergic polymorphic VT (CPVT).

LQTS7/ATS (*KCNJ2*) is caused by defective Kir2.1, a critical component of the inward rectifier potassium current (I_{K1}).[32] Mutations within *KCNJ2* cause ATS,[33] a rare, autosomal dominant disorder (≈1:500,000) characterized by periodic paralysis, mild QTc prolongation, ventricular arrhythmias, and distinctive facial and skeletal dysmorphism.[32] LQTS occurs in 71% of patients with *KCNJ2* mutations, whereas periodic paralysis is present in 64% and dysmorphic features in 78% of probands.[32] Cardiac manifestations include premature ventricular contractions, nonsustained polymorphic VT, bidirectional VT, torsades de pointes, cardiac arrest, and sudden death.[34] Some patients with *KCNJ2* mutations exhibit only arrhythmic phenotype. Nearly 73% of patients with clinical features of ATS and *KCNJ2* mutations have a prolonged terminal T wave downslope,

a wide T-U junction, and a biphasic and large U wave, all reflecting decreased I_{K1} current.[34]

LQTS8/Timothy syndrome (*CACNA1C*) is caused by defective L-type calcium channel, $Ca_V1.2$, which is responsible for the depolarizing calcium current (I_{CaL}). Mutations in *CACNA1* cause Timothy syndrome, a malignant condition characterized by QT prolongation (LQTS8, <0.5% of LQTS cases), T wave alternans, lethal arrhythmias, syndactyly, congenital heart disease, immune deficiency, intermittent hypoglycemia, cognitive abnormalities, and autism.[35] In a study by Splawski et al,[35] 10 of the 17 affected children (59%) died at a mean age of 2.5 years.

LQTS13 (*KCNJ5*) is caused by a defective muscarinic-gated K+ channel (I_{KACh}) current. *KCNJ5* encodes for the G protein-coupled, inwardly rectifying potassium channel subunit Kir3.4.[36] Individuals harboring mutations in *KCNJ5* exhibit only slightly prolonged QTc but have a greater T wave morphology combination score based on asymmetry, flatness, and notch, and a reduced low-frequency/high-frequency ratio of heart rate variability as a reflection of cardiac autonomic imbalance.[37] Only 25% display a QTc >480 milliseconds.

LQTS14 (*CALM1*), LQTS15 (*CALM2*), and LQTS16 (*CALM3*) are caused by defective calmodulin, which modifies the interactions of calcium signal transduction pathway elements with target proteins. In 1 cohort of LQTS patients, calmodulin-related functional variants explained 13% of cases.[38] Compared with a general LQTS cohort, these patients present earlier in life with more profound QT prolongation, premature cardiac arrest, or sudden death,[39,40] and may have overlapping features of LQTS and CPVT.[38]

Prognostic Value

LQTS1 patients ≤40 years of age have been reported to have a higher prevalence of recurrent syncope, aborted cardiac arrest, and sudden death than patients with LQTS2 or LQTS3; however, patients with LQTS3 have a higher lethality of cardiac events, and the cumulative mortality at 40 years of age is similar (6–8%) among patients with LQTS1 through LQTS3 genotypes.[41] In the study by Priori et al,[10] males with either LQTS2 or LQTS3 but not LQTS1 were more likely to become symptomatic before 40 years of age. Cardiac arrest occurred earlier among males with either LQTS1 or LQTS2, than among females. Independent of gender, a QTc ≥500 milliseconds is considered the most important predictor of cardiac events in LQTS1, LQTS2, or LQTS3.[10,42] The risk for cardiac events also varies among carriers of different variants within the same affected gene. As such, LQTS1 patients with transmembrane mutations exhibited longer QTc intervals and had a higher risk of cardiac events than individuals with C-terminal mutations.[17] Moss et al[43] reported that LQTS2 patients who carry *KCNH2* pore region mutations have a twice higher rate of cardiac events than those with mutations in other regions of *KCNH2*. Kapa et al[44] showed that nonmissense mutations in *KCNQ1*, *KCNH2*, and *SCN5A* have a higher probability to cause LQTS (>99%) regardless of location. In contrast, location appears to be critical for pathogenicity of missense mutations. The corresponding percentage of mutations found in definite cases that would cause LQTS was particularly high, reaching up to 100% in the transmembrane/linker/pore regions of *KCNH2*; the linker, pore, transmembrane, and C-terminus of *KCNQ1*; and the transmembrane/linker of *SCN5A*. In a topology-based predictive pathogenicity analysis, Kapplinger et al analyzed the rare variants in the C-terminus of Kv7.1 channel (*KCNQ1*) and identified several highly conserved regions (amino acids 349–391, 509–575, and 585–607) with significantly greater risk.[18]

Mutations that lead to dominant-negative effect (alteration in the gene product so it acts antagonistically and out-competes the wild-type protein) on I_{Ks} or I_{Kr} lead to a more severe LQTS phenotype, as compared to mutations with haploinsufficient behavior.[43] Such severe phenotype is attributed to the marked alteration of the defective ion channel properties, with or without incomplete intracellular processing and defective trafficking of the channel molecule. Rare variants in $Na_V1.5$ localizing to the Domain III/IV (DIII/DIV) interdomain linker have been reported to have a high probability of being pathogenic.[45]

LQTS patients with multiple mutations have been shown to exert more severe phenotype evidenced by longer QTc intervals, higher occurrence of cardiac arrhythmias and a nearly 3.5-fold higher rate of cardiac arrest, as compared to probands with a single or no identified mutation.[12]

Therapeutic Implications

The 2013 Heart Rhythm Society (HRS), European Heart Rhythm Association (EHRA), and Asia Pacific Heart Rhythm Society (APHRS) Expert Consensus recommends β-blockers as first-line prophylactic treatment for all mutation carriers (class IIa), except asymptomatics with a QTc ≤470 milliseconds, in whom decisions may be individualized.[8] β-Blockers alone can lead to up to a 97% reduction in cumulative mortality from LQTS1, and to a lower extent from LQTS2.[46,47]

Lifestyle modifications are an important part of managing LQTS patients. Genetically positive patients, regardless of the phenotype, are advised to avoid QT-prolonging medications (www.crediblemeds.org). Patients with LQTS1 and LQTS2 are instructed to avoid emotional stress and vigorous sports activities, particularly swimming for LQTS1, unless an implantable cardioverter defibrillator (ICD) is implanted, whereas those with LQTS3 do not need exercise restriction. However, patients with LQTS3 should be advised to avoid abrupt cessation of rigorous physical exercise, which may cause vagal over-activation and predispose to arrhythmias.

Patients with LQTS2 are recommended to avoid arousal sources, particularly when resting, such as alarm clocks or loud telephones in the bedroom. Fatality risk, however, remains substantially high in patients with Jervell–Lange–Nielsen syndrome, in which conventional doses of β-blockers have limited efficacy, and ICD therapy is usually indicated.[48]

For many years, the use of β-blockers in LQTS3 has been controversial. Recent studies have shown that β-blocker therapy is associated with an 83% reduction of major cardiac events in females, but not in males (who had fewer events)[42]; however, their use requires vigilance because slow heart rate may induce rate-dependent ventricular arrhythmias.[23] Nadolol (1 mg/kg) seems to be the best treatment option for LQTS patients, but unfortunately, it is not available in many countries.

Several sodium channel blockers may be useful in LQTS3. In a recent study, mexiletine shortened the QTc interval and caused a major reduction of life-threatening arrhythmias in LQT3 patients.[49] However, some mutations have a dual effect on the channel, reduced peak current (loss of function), and increased late current (gain of function); thus, patients with important loss of function may not be candidates to sodium channel blocker therapy. If no functional data are available on the specific variant, it is recommended to perform a drug challenge test under continuous ECG monitoring before prescription of sodium channel blockers to assess both QTc response and the potential proarrhythmic effect or eventual Brugada syndrome (BrS)-type ECG pattern.[50,51]

CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

CPVT is an inherited arrhythmic disorder characterized by adrenergically mediated polymorphic or bidirectional VT that may degenerate into VF and cause SCD in patients with structurally normal hearts (Fig. 2).[52] The prevalence of CPVT is roughly estimated to be 1 in 10,000.[53] Since the initial description of this severe CPVT phenotype, it has become evident that some patients have

less aggressive disease and outcome. Nevertheless, when symptoms develop early in life, the prognosis is lethal if untreated.

Diagnosis of CPVT

CPVT is diagnosed in the presence of exercise- or emotion-induced bidirectional VT, characterized by alternating 180°-QRS axis on a beat-to-beat basis, or polymorphic VT in patients with structurally normal hearts and normal resting ECGs; and/or identification of a pathogenic mutation in *RyR2* or homozygous mutations in *CASQ2*.[1,8] Several cardiovascular conditions may produce clinical features resembling CPVT. Patients with LQTS1 experience exercise-related arrhythmias or syncope. However, they do not have the typical inducible arrhythmias during exercise stress test, as seen in CPVT. Bidirectional VT has also been reported in patients with ATS[54]; however, the prolonged QT interval, prominent U waves, lack of association of arrhythmias with adrenergic triggers, the presence of extracardiac manifestations, and *KCNJ2* mutations identified by the genetic test allow us to distinguish ATS from CPVT.

Genetic Basis of CPVT and Implications of the Genetic Test in CPVT

Known CPVT-associated genes are involved in the calcium homeostasis of cardiac cells.[55,56] The cardiac ryanodine receptor RyR2 (*RyR2*) is the principal component of the calcium channel located on the sarcoplasmic reticulum (SR) of cardiomyocytes and functions as the main control for the calcium-induced calcium release. Mutations in *RyR2* are found in up to 60% of patients with strong CPVT phenotype (CPVT1) and autosomal dominant inheritance.[57] *CASQ2* encodes for cardiac calsequestrin, a luminal calcium-binding glycoprotein that effectively buffers the SR calcium and normally maintains free calcium concentrations below the inhibitory level of SR/endoplasmic reticulum Ca^{2+} ATPase and, thereby promotes calcium reuptake into the SR.[58] Compound heterozygous or homozygous *CASQ2* mutations account for up to 5% of CPVT cases (autosomal recessive; CPVT2).[1] Autosomal dominant inheritance has been reported for *CASQ2*-CPVT in a single family.[59] Mutations in *RyR2* or *CASQ2* cause uncontrolled calcium release from the SR, which leads to bidirectional or polymorphic VT mediated by delayed after-depolarizations and triggered activity.[55]

Mutations in *TRDN*,[60] *CALM1*,[61] and *CALM3* have been detected in individuals with hallmark features of CPVT,[62] sometimes in association with prolonged QT intervals. Mutated triadin (*TRDN*) renders calsequestrin unable to inhibit the RyR2 activity, allowing calcium leaks from the SR and development of clinical features of CPVT, with a recessive mode of transmission.[60] In 2007, an early-onset lethal form of CPVT with recessive inheritance in a consanguineous Arab family had been linked to a new locus first mapped on chromosome 7p14-p22,[63] which had been later corrected and mapped to the *TECLR* (4q13 locus).[64] Recently, *TECRL* and *CALM2* mutations have been identified in cardiac arrest survivors with clinical features of both LQTS and CPVT.[64,65]

Diagnostic Value

The diagnostic yield of genetic test in CPVT is nearly 60% (Fig. 3).[1] Testing of at least *RyR2* and *CASQ2* genes is recommended for patients in whom a clinical index of suspicion has been established.[1] A positive result, besides confirming the diagnosis, is very useful to identify other affected family members at risk for SCD (Table 2).[1,8]

Genotype–Phenotype Correlation

Though CPVT typically presents with unremarkable cardiac imaging and baseline ECG, several exceptions have been reported. *RyR2* mutation carriers have lower baseline heart rate, and 19% show sinus bradycardia.[66] Moreover, a large genomic deletion in exon 3 of *RyR2* produced an extended clinical profile including sinoatrial node and atrioventricular dysfunction, AF, atrial standstill, and dilated cardiomyopathy, in addition to the classic CPVT phenotype.[67] Mutation localization has been associated with severity of the phenotype; mutations in the C-terminal channel-forming domain have been associated with an increased risk for nonsustained VT, whereas central domain mutations have been more frequently associated with supraventricular arrhythmias other than sinus bradycardia.[66] Studies in CPVT patients with and without *RyR2* mutations showed that both groups have average onset of symptoms between 7 and 12 years.[52] Clinical features of *CASQ2*- and *RyR2*-mediated CPVT appear similar; however, because *CASQ2*-related cases are very rare, more reliable data may become available with identification of more affected individuals.[56]

Prognostic Value

When a clear mutation has been identified in *RyR2* in an asymptomatic person, it has important prognostic value. The penetrance of *RyR2*-mediated disease is nearly 83%.[68] CPVT patients generally have a poor prognosis if left untreated, as up to 50% will suffer SCD before 20 years of age,[69] hence undetected CPVT presents a frequent cause of unexplained SCD in the young.[70] A carrier of a heterozygous *CASQ2* mutation confers low or no risk of developing the disease.

Therapeutic Implications

Family members of CPVT patients, who have a clearly pathogenic mutation in *RyR2* or a homozygous/compound heterozygous mutation in *CASQ2*, have an indication for treatment with β-blockers (class IIa).[8] The recommended β-blocker is nadolol 1 mg/kg.[8] Knowing the precise genetic diagnosis allows for the use of certain antiarrhythmic drugs or possibly gene therapy in the near future.

The management of CPVT is based on the following strategies: reducing myocardial adrenergic activation with β-blockers; preventing spontaneous calcium release from SR and triggered activity; left cardiac sympathetic denervation; and/or ICD as a back-up strategy in high-risk subjects.[8] Therapy with flecainide prevents ventricular arrhythmias in patients with CPVT not controlled by β-blockers.[71,72] In a recent randomized clinical trial, therapy with flecainide plus a β-blocker significantly reduced ventricular ectopy during exercise compared with placebo plus β-blocker or a β-blocker alone.[73] *KCNJ5*-mediated CPVT may be more responsive to therapy with flecainide or mexiletine rather than β-blockers.[74] In contrast, the protective effect of left cardiac sympathetic denervation has been demonstrated more clearly for patients with *RyR2*-CPVT than those with *CASQ2*- or *KCNJ5*-mediated CPVT.[75]

Gene-specific therapy in animal models of CPVT has been performed with optimistic results. Viral gene transfer of wild-type *CASQ2* into the heart of R33Q mice induced functional long-term expression of calsequestrin, and thereby prevented and reverted severe manifestations of CPVT.[76] Interestingly, allele-specific silencing by ribonucleic acid interference prevented life-threatening arrhythmias in CPVT mice model carriers of the heterozygous mutation *RyR2*-R4496C.[77] These promising findings demonstrate that gene therapy might be an appealing novel therapeutic option for CPVT. Gene therapy is currently being explored at the clinical level.

J WAVE SYNDROMES

J wave syndromes consisting of the BrS and early repolarization syndrome (ERS) are described by an accentuation of the J wave on the ECG and life-threatening ventricular arrhythmias.[78] The early repolarization pattern on the ECG (distinct J-point elevation, or a notch or slur of the terminal part of the QRS with or without an ST-segment elevation) is frequently seen in young and apparently

healthy individuals, particularly athletes, with a prevalence up to 40%. In most cases, this is a benign ECG feature,[78] but in some cases, an association with the development of polymorphic VT and VF, both in animals and in humans, has been reported.[79,80] These findings challenged the benign nature of early repolarization pattern, and it was subsequently referred to as ERS when associated with VT/VF in the absence of apparent heart disease.[78] BrS and ERS share similarities with respect to their clinical manifestations and response to pharmacologic therapy, suggesting a similar pathophysiology.[78] The 2 clinical entities also share a genetic substrate; so far 7 culprit genes have been implicated in ERS, all of which, with the exception of *CACNA2D1*, have also been linked to BRS.[78] It is possible that some or all of the knowledge on genetics of BrS can be helpful for the diagnosis and management of ERS patients and their families. So far, the clinical implications of the genetic test are relatively better established for BrS[78]; therefore, in this section, we will focus on BrS.

Brugada Syndrome

BrS is characterized by a typical ECG pattern of coved-type ST-segment elevation with successive negative T wave in the right precordial leads (V_1 to V_3) with or without cardiac conduction delays at different levels, and susceptibility to ventricular tachyarrhythmias and SCD (Fig. 2).[78] BrS frequently manifests in the 3rd or 4th decade of life with ventricular arrhythmias or SCD typically occurring during sleep.[81] The prevalence of BrS is markedly eightfold higher in males, who also have a 3.3-times higher risk for syncope, ICD shock, and SCD than females.[81] The global prevalence of manifest BrS is estimated at 1–5 per 10,000, but the true prevalence might be higher due to an often silent course and intermittent ECG pattern.[82] The manifest form is more prevalent in Asian and Southeast Asian countries, especially in Japan, Thailand, and the Philippines, where it is the major cause of SCD in the young.

Diagnosis of BrS

The diagnosis of BrS is based on its characteristic ECG phenotype (resting 12-lead ECG or provocative drug challenge testing), clinical, and family history.[1]

Genetic Basis of BrS and Implications of the Genetic Test in BrS

Genetic bases are identified in nearly 30–35% of BrS cases (Fig. 3). Mutations in at least 20 genes have been implicated in BrS.[83] The majority of BrS cases are sporadic.[84]

Loss-of-function mutations in *SCN5A* account for about 30% of BrS cases, and mutations in other genes collectively account for an additional 5%.[85,86] Mutations in $Na_V1.5$ interacting proteins, such as its β-subunit gene, have been shown to cause BrS through their modifier effect on the $Na_V1.5$ (*SCN5A*) function.[87–89] Mutations in *SCN10A*, *RANGRF*, *GPD1L*, and *SLMAP* independently caused BrS through reducing the $Na_V1.5$ surface membrane expression and the I_{Na} current.[90–93] Liu et al[94] identified *TRPM4* mutations in 6% of 248 BrS patients who tested negative for *SCN5A* mutations. Additionally, Cerrone et al[95] found that in some cases, mutations in desmosomal plakophilin 2 (*PKP2*), which are associated with arrhythmogenic right ventricular cardiomyopathy (ARVC), can be part of the BrS molecular substrate by causing a drastic reduction in I_{Na} specifically at the intercalated disc as a result of reduced number of functional channels.

Gain-of-function mutations in potassium channel genes *KCND3* (encodes Kv4.3), *KCNE5* (X-linked), and *KCNE3* (through interacting with Kv4.3) independently resulted in an increase of the cardiac transient outward potassium current (I_{to}), and produced BrS phenotype in a few cases.[96–98] *KCNJ8* and *ABCC9* encode Kir6.1 and sulfonylurea receptor subunit 2A, respectively, which compose the hetero-octameric structure of the ATP-sensitive potassium channel (KATP) channel.[99] Gain-of-function mutations in *KCNJ8* or *ABCC9* have been reported in association with severe BrS phenotype.[100,101] Among 236 Japanese BrS patients, 4 probands, of which 3 exhibited short QT interval, were found to have *KCNH2* mutations.[102]

Loss-of-function mutations in calcium channel subunit genes *CACNA1C, CACNB2b*, and *CACNA2D1* cause a decrease in the I_{CaL} current, resulting in a phenotype of BrS combined with short QTc interval.[103,104]

Increasing evidence suggests that except for its *SCN5A*-mediated type, BrS is probably an oligogenic disease,[105] and clinical studies on large cohorts are required to determine the role of the minor genes in the pathogenesis of BrS. It is possible that BrS represents the final phenotype of multiple pathophysiologic mechanisms sharing the same common pathway. The low penetrance, heterogeneous background, and high proportion of genetically negative BrS cases favor this hypothesis. Recently, several studies have reported a clinical and genetic overlap between BrS and ARVC as evidenced by ARVC-specific structural and ECG abnormalities and identification of *PKP2* mutations in BrS patients, and a BrS-specific ECG pattern in ARVC patients in response to ajmaline challenge test.[95,106,107] According to Nademanee et al,[108] the underlying electrophysiologic mechanism of BrS is delayed depolarization over the anterior aspect of the right ventricular outflow tract epicardium. Catheter ablation over this abnormal area resulted in normalization of the BrS-specific ECG pattern and prevented VT/VF in high-risk BrS patients.[108]

Diagnostic Value

Comprehensive or *SCN5A* genetic testing is considered useful (class IIa) for any patient with clinical suspicion of BrS. Mutation-specific genetic testing is recommended for family members after identification of a causative mutation in the index patient (class I),[1] and allows for presymptomatic diagnosis in relatives at risk who need further clinical follow-up and preventive measures, i.e., antiarrhythmic medications, avoiding drugs with sodium channel blocking activity, avoiding excessive alcohol intake, prompt treatment of fever with antipyretics, etc.

Genotype–Phenotype Correlation

In a study by Smits et al,[109] patients with *SCN5A*-mediated BrS had a significantly longer PQ interval and longer His-ventricular conduction time (HV) than patients with non-*SCN5A* BrS. A PQ interval of ≥210 milliseconds and HV interval of ≥60 milliseconds were predictive for the presence of a *SCN5A* mutation. This finding was validated by a recent study in which BrS patients with *SCN5A* mutations more frequently exhibited conduction abnormalities, than those without.[110]

The exerted ECG pattern can often be a clue for underlying genotype in BrS patients. Short QT interval often indicates mutations in *CACNA1C* or *CACNB2b*, or rarely *CACNA2D1*.[83,104]

Prognostic Value

There are limited and conflicting data on the role of genetics in BrS prognosis. In the France, Italy, Netherlands, Germany (FINGER) BrS registry, *SCN5A* mutation status was not an independent risk factor for cardiac events (syncope or SCD),[111] whereas Nishii et al[112] and Yamagata et al[110] found a significantly higher rate of cardiac events and lower shock-free survival rate in *SCN5A* mutation carriers. In an analysis considering the mutation types, BrS patients with a nonsense or frameshift mutation in the *SCN5A* gene were more likely to develop prolonged PR and QRS intervals (increased conduction delay at different levels in the heart) and present with syncope, than those harboring missense *SCN5A* mutations.[113]

Therapeutic Implications

Currently, genetic test in BrS has no direct therapeutic implication; however, asymptomatic carriers of clear mutations can be subjected to regular control and can advise about potential arrhythmia triggers.

SHORT QT SYNDROME

Short QT syndrome (SQTS) is a very rare and highly lethal heritable cardiac channelopathy characterized by brief QT intervals on the ECG and high susceptibility to atrial and ventricular arrhythmias and SCD (Fig. 2).[114,115] The true incidence is unknown. To date, approximately 100 cases of SQTS have been described. In a recent study, a QTc ≤330 milliseconds has been observed in 0.05% of the population (using Bazett formula for correction), but these individuals were asymptomatic and had low-to-intermediate risk of SQTS based on clinical and family history.[116] This suggests that the prevalence of true high-risk SQTS might be even lower. The underlying molecular substrates are short atrial and ventricular refractory periods leading to increased vulnerability to VF.[117] Patients can present with palpitations or syncope; nevertheless, cardiac arrest at rest can be the first manifestation of the disease in up to 40% of cases.[113] Survivors of cardiac arrest have a high recurrence rate of potentially fatal arrhythmias. Male and female genders have similar mortality and prevalence of the disease.[115,118]

Patients with SQTS, regardless of the genetic status, and carriers of SQTS-associated mutations, regardless of QTc duration, commonly exhibit AF.[118] Interestingly, AF has also been noted in children and adolescents with SQTS; therefore, SQTS should be considered in youngsters with idiopathic (lone) AF.

Diagnosis of SQTS

Gollob et al[119] proposed a diagnostic score to assess the likelihood of having SQTS. The HRS/EHRA/APHRS Expert Consensus suggested the diagnosis of SQTS in the presence of QTc ≤330 milliseconds.[8] SQTS can also be diagnosed in individuals with a QTc <360 milliseconds, who have at least one of the following additional criteria: a pathogenic mutation in culprit genes, family history of SQTS or of SCD by 40 years of age, or survival of a VT/VF episode in the absence of other cardiac disease.[8] Other ECG characteristics include peaked T waves in precordial leads with either short or no ST-segment. The QT interval in SQTS is not only too short but also fails to adapt to heart rate with reduced or absent shortening during exercise.[117]

Genetic Basis of SQTS and Implications of the Genetic Test in SQTS

The first gene described in SQTS was *KCNH2* (SQTS1). Mutations in *KCNH2* dramatically increase I_{Kr} (opposite to the loss-of-function variant in LQTS2), leading to heterogeneous abbreviation of action potential duration and refractoriness, and reduced channel affinity to class III antiarrhythmics.[120]

So far, 5 additional genes have been linked to SQTS.[8,121] The subtypes SQTS1, SQTS2, and SQTS3 are caused by gain-of-function mutations in potassium channel genes *KCNQ1*, *KCNH2*, and *KCNJ2*,[120,122,123] which are also linked to LQTS2, LQTS1, and LQTS7, respectively, whereas SQTS4, SQTS5, and SQTS6 subtypes are caused by loss-of-function mutations in calcium channel genes and can present as either isolated SQTS (*CACNA2D1*)[121] or clinical features of both BrS and SQTS (*CACNA1C, CACNB2*).[104] *KCNH2* mutations have been described in families with paroxysmal AF and SQTS.[124] Based on the currently available limited data, the penetrance of SQTS is estimated to be around 80%.[118]

Diagnostic Value

The yield of genetic testing has been reported to be nearly 40% in a combined analysis of all previously reported SQTS cases[118] but has been lower (23–27%) in smaller cohorts (Fig. 3).[119,125] Screening of *KCNH2*, *KCNQ1*, and *KCNJ2* is recommended as part of the diagnostic evaluation in individuals in whom a clinical suspicion for SQTS has been established based on clinical and family history, and electrocardiographic phenotype.[1] Mutation-specific screening is recommended in family members of patients with a genetically positive SQTS (Table 2).

Genotype–Phenotype Correlation

Despite the rarity of SQTS, gene-specific phenotype markers are beginning to emerge. The T waves tend to be symmetric in SQTS1, but asymmetrical with a less steep ascending limb followed by a rapid descending limb in SQTS2 to SQTS4 (Fig. 2).[126] In SQTS2, inverted T waves are commonly seen. In SQTS5, a BrS-type ST-elevation in the right precordial leads V_1 and/or V_2 may be seen at baseline or after administration of sodium channel blockers.[126]

There is no difference in QT duration between gene-specific SQTS groups.[118,127] Patients with SQTS1 are typically diagnosed during the 4th decade of life, whereas patients with other SQTS genetic profiles usually present before 20 years of age.[118] SQTS2 patients have a strikingly higher prevalence of sick sinus syndrome and bradycardia (SQTS2: 75% vs non-SQTS2: 9%) and AF, compared to non-SQT2 patients (SQT2: 63%; non-SQTS2: 21%).[118]

Prognostic Value

Risk stratification remains the main challenge in SQTS patients. The scoring system of Gollob et al[119] unfortunately showed low sensitivity, predicting low probability of arrhythmic events in 63% of survivors of cardiac arrest in a study by Mazzanti et al.[115] The uncertainty further increased after 1 study where SQTS patients with QTc ≤320 milliseconds neither had a history of syncope nor familial event, or experienced any fatal cardiac event during a mean follow-up of 5 years.[128] Another study reported the QTc value as the only risk factor for arrhythmic events in general SQTS population (QTc, <360 ms).[125] A possible explanation for this discrepancy could be the presence of more malignant founder mutations in the cohort investigated by Mazzanti et al,[115] but it is more likely that, similar to other channelopathies, gene–gene interactions and posttranslational factors influence the outcome.

Therapeutic Implications

The genetic test in SQTS is useful mainly for family members; when positive, cascade screening can be performed to detect relatives at risk of SCD.[8] But so far, no specific therapy is available for the different genetic forms.

PROGRESSIVE CARDIAC CONDUCTION DISEASE

Progressive cardiac conduction disease (PCCD) is a slow, degenerative process that affects the cardiac conduction system with or without concomitant structural heart disease.[129] The disease is caused by a progressive alteration in impulse propagation through the His-Purkinje system due to myocardial degeneration, increased collagen turnover in the myocardium and fibrosis in the conduction system, leading to conduction abnormalities at various levels.

Diagnosis of PCCD

PCCD is diagnosed clinically in the presence of unexplained progressive conduction abnormalities in young individuals (<50 years of age).[8] Imaging modalities such as 2D echocardiography or cardiac magnetic resonance imaging should be performed to identify

potential concomitant heart disease.[8] Genetic testing may be considered (class IIb) in evaluating patients with isolated PCCD or PCCD with concomitant structural heart disease (particularly early-onset forms), especially in the presence of a positive family history of conduction abnormalities, pacemaker implants, or SCD.[1,8] Mutation-specific genetic testing is recommended (class I) for appropriate relatives after identification of a PCCD-causative mutation in the proband.[1]

Genetic Basis of PCCD and Implications of the Genetic Test in PCCD

PCCD in structurally normal heart ("isolated PCCD") is caused by mutations in *SCN5A*, *SCN1B*, *SCN10A*, *TRPM4*, *GJA5*, and *KCNK17*. There is a consistent overlap between BrS and PCCD, which can be explained by the shared pathogenesis as indicated by loss-of-function *SCN5A* mutations.[130] Mutations in *SCN10A* ($Na_V1.8$) lead to atrioventricular (AV) conduction defects and BrS due to its interaction with the promoter of *SCN5A*.[131] Additionally, loss-of-function mutations in *SCN1B* can cause BrS with conduction disease through reduced current density and enhanced slow inactivation of the channel.[132]

Mutations in *TRPM4* have been recently implicated in autosomal dominant PCCD.[133] Makita et al[134] demonstrated a causal relationship between functional alteration in cardiac gap junction protein connexin-40 (*GJA5*) and PCCD with malignant ventricular arrhythmias. In 1 patient with PCCD, a germline mutation in *GJA5* led to marked reduction of junctional conductance and diffused localization of immunoreactive proteins in the vicinity of the plasma membrane without formation of gap junctions.[134]

PCCD with concomitant structural/congenital heart disease has been previously associated with mutations in genes essential for cardiac morphogenesis. Alteration in *TBX5* and *NKX2.5* genes has been shown to cause defective expression of connexin-40 and incomplete development of the specialized conduction system.[135]

Diagnostic Value

The diagnostic implication of genetic test in PCCD lies in distinguishing genetically mediated disease from acquired forms. Genetic testing in PCCD will also help to identify high-risk patients with potential overlap syndromes and/or those at risk of other cardiac diseases (Table 2).

Genotype–Phenotype Correlation

SCN5A mutations can produce symptoms early in life, and additional rhythm disturbances such as AF, atrial flutter, or overlap syndrome.[136] Mutations in *NKX2.5* have been reported in association with secundum type atrial septal defect, tetralogy of Fallot, truncus arteriosus, L-transposition of great arteries, double-outlet right ventricle, interrupted aortic arch and hypoplastic left heart syndrome, with or without conduction defects,[137] ventricular noncompaction, and sudden death.[138] Mutations in *TBX5* cause Holt–Oram syndrome, an autosomal dominant disorder that affects the bones and the heart.[139] Cardiac manifestations include conduction defects with or without concomitant atrial or ventricular septal defects, bradycardia, or AF.

When PCCD is associated with hypertrophic cardiomyopathy and Wolff–Parkinson–White syndrome, *PRKAG2*-mediated disease should be suspected.[140] Mutations in *LMNA* have been previously associated with PCCD with and without muscular dystrophy and/or dilated cardiomyopathy. Severe arrhythmias and SCD in these patients may precede the development of cardiomyopathy/muscular dystrophy phenotype. In *LMNA*-mediated disease, progressive atrioventricular block is a risk factor for ventricular arrhythmias.[141]

Prognostic Value

Meregalli et al[113] demonstrated a correlation between *SCN5A* mutation type and the clinical and ECG phenotype in BrS or PCCD probands. Patients with either a truncation mutation or a severe loss-of-function missense mutation causing >90% reduction in peak I_{Na} had a significantly longer PR interval than patients with missense mutations causing ≤90% reduction in peak $I_{Na.}$ Truncation mutations were associated with a significantly higher rate of syncopal episodes compared with missense mutations. It is also known that *GJA5*-mediated PCCD has early onset and is associated with premature SCD.[134] Patients with *LMNA* mutations and left ventricular dysfunction also have a high risk of SCD. Patients with *PRKAG2* mutations may have ventricular preexcitation or the Wolff–Parkinson–White syndrome caused by nodoventricular/fasciculoventricular accessory pathways; therefore, ablation is at high risk for iatrogenic atrioventricular conduction blocks.[142]

Therapeutic Implications

Due to the overlap with BrS and idiopathic VF, patients with *SCN5A*-mediated PCCD should receive active treatment of fever to avoid fever-induced ventricular arrhythmias. Targeted genetic screening of first-degree relatives of genetically positive index patients allows prospective follow-up of asymptomatic mutation carriers.

CONCLUSIONS

Genetic testing is currently an essential component in the evaluation of patients with suspected inherited arrhythmia syndromes. Understanding the molecular substrate of these diseases improves the diagnosis, allows tailored therapy and better risk stratification. Genetic testing in family members allows the identification of individuals who need further surveillance to prevent SCD, or even lifestyle changes. Ongoing studies are expected to improve the current knowledge on genotype–phenotype correlation in these genetically heterogeneous cardiac diseases, with a promise of individualized, "mutation-specific therapy." The advancement of in vivo experiments will spur the discovery of drugs that target mechanisms underpinning these malignant arrhythmias. The promising results of gene therapy in animal models will optimistically open doors to the development of effective mutation-specific therapies in patients with inherited arrhythmia syndromes.

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